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Can we control tuberculosis in high HIV prevalence settings?

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Summary The overlap between the epidemiology of HIV and tuberculosis and consequent rapid rise in numbers of patients with tuberculosis in many African countries has put a huge burden on health systems. The stigma of HIV has increased the existing stigma surrounding tuberculosis. There are three mechanisms by which we may reduce the number of cases of tuberculosis in a community: reducing transmission of tuberculosis, reducing reactivation of latent tuberculosis infection and reducing HIV transmission. Reinforcing the existing health service to find more cases, active case-finding in communities or enhanced case-finding in specific groups will reduce transmission of tuberculosis. However, health services that find it difficult to find cases efficiently will also find it difficult to support patients throughout treatment to achieve a cure. Partnership with traditional healers, community-based organizations and private practitioners could reduce this burden. Reactivation of tuberculosis among people living with HIV can be reduced by tuberculosis preventive therapy or by antiretroviral therapy. Programmes that identify people living with HIV can also implement enhanced tuberculosis case-finding increasing the benefits of the programme. However, the impact of widespread use of antiretroviral therapy may be to increase the number of people in a community who are mildly immunocompromised and the incidence of tuberculosis at a community level might rise. Any strategy that successfully reduces HIV transmission will benefit tuberculosis control, since around a third of all HIV-positive individuals will develop tuberculosis before they die. To control tuberculosis in high HIV prevalence settings, we must strengthen health systems to include not only expansion of the DOTS strategy but also full-blooded implementation of voluntary counselling and testing, enhanced and active tuberculosis case-finding, preventive therapy and better care for people living with HIV including antiretroviral therapy. The approach needed to control tuberculosis needs also to be integrated into broader development and poverty reduction goals.

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HIV is the greatest risk factor for tuberculosis ever known. Infection with HIV leads to both greatly increased rate of reactivation of latent tuberculosis infection¹ and a greatly enhanced susceptibility to progression to active tuberculosis following new infection.^{2–5} Current strategies for the control of

tuberculosis are not sufficient in these dually burdened areas and we need to identify additional strategies and new approaches to control tuberculosis in high HIV prevalence settings.

Epidemiology of the dual epidemic of tuberculosis and HIV

Before the advent of HIV, 10% of those infected with tuberculosis would be expected to progress to

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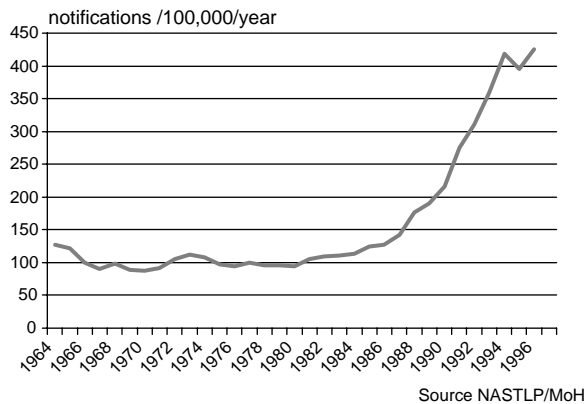


Figure 1 New cases of tuberculosis in Zambia—notification rate/100,000/year 1964–1996.

active tuberculosis disease over their lifetime, of whom about one-half would have infectious, usually sputum smear positive, disease.⁶ It follows that if one infectious case of tuberculosis successfully infected 20 other people, one was likely to develop smear positive or infectious tuberculosis and the disease would be maintained at a stable level in the community. When HIV is added into the equation the same infectious individual will still infect 20 others but some of these will be HIV infected. If we consider a scenario where HIV prevalence is 10% (a situation exceeded in some of the worst affected countries) then two of the infected contacts will be HIV positive. These HIV-positive individuals, once infected with tuberculosis, will be expected to progress to active disease more rapidly and more cases of active disease will occur in addition to the cases from the 18 HIV-negative individuals. Even allowing for a greater proportion of non-infectious (smear negative or extrapulmonary) tuberculosis this results in a net reproduction rate greater than 1 and an expanding epidemic.

The countries of the world with the highest HIV prevalence rates are also those with high rates of tuberculosis and therefore it is these countries that bear the burden of this dual epidemic. In one such country, Zambia, the tuberculosis notification rate was stable throughout the 1960s and 1970s showing a degree of control of tuberculosis. In the 1980s, HIV spread rapidly through southern Africa and the case detection of tuberculosis quadrupled (Fig. 1). Zambia is not alone. No country with a high HIV prevalence is managing to contain tuberculosis. Figure 2 shows a linear correlation between the UNAIDS' estimates of adult HIV seroprevalence in African countries and the WHO's estimates of tuberculosis incidence in the same countries.^{7,8}

Impact of HIV on tuberculosis control

Increasing the numbers of tuberculosis cases puts an increased burden on a health system that is often already pushed to its limits. Tuberculosis control requires direct observation of therapy for at least the intensive phase of therapy and in many countries health services are becoming swamped. This added burden is not the only way in which HIV impacts on tuberculosis control. In communities with high prevalence of HIV the diagnosis of tuberculosis is more challenging. More individuals have smear negative disease, difficult to diagnose in resource-poor settings where sputum smear is the mainstay of detection. The symptoms of tuberculosis and other HIV-related lung diseases can be very similar resulting in both over-diagnosis—increasing the burden on resources, and under-diagnosis—missing out on the opportunity to cure tuberculosis.⁹ The sensitivity and/or specificity of more sophisticated diagnostic techniques, such as chest X-rays¹⁰ or serological tests^{11,12} are reduced in an HIV-infected population exacerbating the difficulty of making an accurate diagnosis.

In the most impoverished countries, treatment of tuberculosis with thiacetazone has largely been abandoned due to the high rates of adverse events seen in HIV-positive individuals,^{13,14} while in the richer countries the most effective regimens, that are based on 6 months of rifampicin are sometimes avoided to allow a wider choice of antiretroviral therapy in those with advanced HIV disease.¹⁵ Despite the long history of evidence-based treatment in tuberculosis, many patients are now receiving regimens that have never undergone randomized controlled trials.

Although the rate of treatment failure in HIV-positive and -negative individuals with tuberculosis is similar, recurrent tuberculosis does appear to be more common in high HIV-prevalent settings. This may be due in part to less effective regimens being used in treatment¹⁶ but re-infection is also more common in HIV-positive individuals.¹⁷

Drug resistant tuberculosis is increasing worldwide.¹⁸ While there is limited evidence that drug resistance occurs more readily in an HIV-infected individual, there have been outbreaks of both sensitive and drug-resistant tuberculosis within HIV-positive communities indicating the potential for nosocomial or institutional transmission.^{19,20} Nosocomial transmission is also the likely explanation for the high rate of tuberculosis observed in nurses on the medical wards in Malawi compared to those working in less risky areas.²¹

Tuberculosis mortality rates are also increasing in high HIV-prevalent settings.^{22,23} This observation is

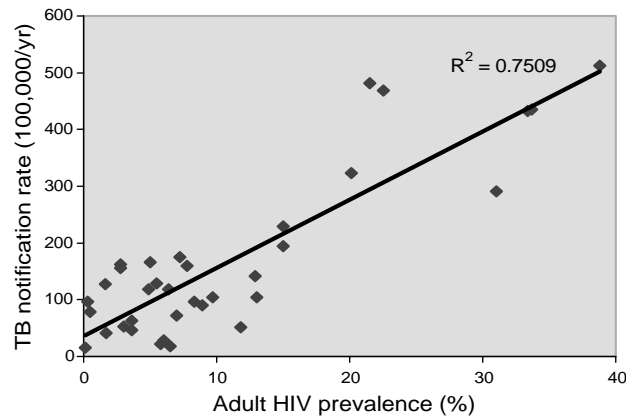


Figure 2 UNAIDS estimates of adult HIV seroprevalence and WHO estimates of tuberculosis incidence for African countries 2001–2002.

not just one made by the medical profession, but is well known in the population as well. A typical “successful” national tuberculosis control programme in Southern Africa based on the DOTS (directly observed therapy, short-course) strategy has therefore seen a three- or fourfold rise in the number of notified cases, over the past decade, with up to one-third of all new patients dying before the end of treatment. It is not surprising that communities and health care workers are sceptical of claims that DOTS is the “cure for all” promoted by the STOP-TB partnership as the theme for World TB day in 2001. Furthermore, it is not only tuberculosis patients who are dying. The mortality among health care workers has a direct impact on the supervision and delivery of tuberculosis services.²⁴

The stigma of HIV has increased the existing stigma surrounding tuberculosis.^{25–27} In Zambia, many communities speak of the “new tuberculosis” or “tuberculosis of the bones” as a euphemism for tuberculosis associated with HIV or just HIV itself. An individual diagnosed with tuberculosis will often be suspected of having HIV, which can lead to discrimination and ostracization. It may also lead to patients presenting late to the health services for fear of being labelled as HIV positive.²⁸ Health care workers also fear and stigmatize tuberculosis. Many of these same health care workers are also HIV infected, although few know their status, and because of the stigma fewer still are willing to be HIV tested.

Finally, HIV increases the vicious spiral that already exists between tuberculosis and poverty.^{29–31} Tuberculosis is recognized to be associated with poverty, overcrowding and malnutrition. Tuberculosis itself impoverishes a family by increasing health care costs^{32,33} and removing the earning capacity of an individual.³⁴ HIV is also fuelled by poverty and also causes the double impoverishment

of reduction in earning capacity at a time when the demands of health-related expenditure are rising. Poverty and stigma act together to increase transmission of tuberculosis and HIV.

How can we control tuberculosis?

To control tuberculosis we need to reconsider all the options available and think more broadly than has been previously the case. The existing strategy for tuberculosis control is DOTS. This strategy relies on detecting the most infectious cases as they pass through the existing health infrastructure and ensuring that adequate treatment with a short course rifampicin-containing regimen is taken. This strategy is succeeding in reducing both mortality and prevalence of tuberculosis in areas with low prevalences of HIV^{35–37} and it is imperative that it is continued and enhanced to cope with the increased burden in high HIV prevalence settings. Expanding DOTS and ensuring high-quality services requires sufficient human and fiscal resources.

However, what is clear is that DOTS is not enough and further measures must also be taken.³⁸ There are three mechanisms by which we may reduce the number of cases of tuberculosis in a community: reducing transmission of tuberculosis, reducing reactivation of latent tuberculosis infection and reducing HIV transmission.

Reducing transmission of tuberculosis

DOTS

The DOTS strategy reduces transmission of tuberculosis by catching infectious patients as they

present to existing health facilities and rendering them non-infectious by efficient anti-tuberculosis chemotherapy. A series of studies from Kenya prior to the HIV era demonstrated that the large majority of those in a community who have sputum smear positive tuberculosis have indeed passed through the government health services, often several times without a diagnosis being made.^{39–41} With the rising burden of morbidity, poor conditions of service of health care workers and consequent low morale, it is not surprising that the situation is no better in the era of HIV. In Lusaka, patients presenting to urban clinics with a cough for more than 3 weeks or haemoptysis were often not asked to produce sputum samples. Even if they were asked to, many never brought a sample, particularly if there was no local laboratory, which meant that they were being asked to take their samples to the central hospital—a significant cost in both time and money for many people. Of 514 patients, only 30% had the result of sputum microscopy documented in the laboratory registers.⁴² The rapid rise in sputum smear negative tuberculosis exacerbates the problems of making accurate prompt diagnoses and in most peripheral diagnostic centres, there are neither the equipment to make chest radiographs nor the expertise to interpret them correctly. Reinforcing the existing health service to find more cases using the DOTS strategy would certainly help to reduce transmission of tuberculosis.

Reinforcing the existing health service might also increase the confidence of patients to come forward and use the service earlier. In many countries, patients who are tuberculosis suspects face significant delays. Delays in diagnosing tuberculosis significantly increase transmission of disease. Health systems research in Zambia shows that the delay in presenting to health services is primarily fuelled not by ignorance of the disease, but by the expectation of poor services and the fear of stigma and discrimination by health workers.⁴³ However, in some settings with a high prevalence of HIV and high rates of tuberculosis, even with well organized and resourced tuberculosis services that are achieving cure rates above the DOTS target of 85%, the majority of tuberculosis is still due to ongoing transmission.^{44,45}

Prevalence surveys also suggest that there may be large numbers of undiagnosed cases of active disease in the community^{46,47} although other South African studies have found many fewer.⁴⁸ If the passive case-finding advocated within the DOTS approach is not enough to prevent ongoing transmission of tuberculosis, could active case finding be incorporated into programmes? While screening of

whole populations is a daunting challenge, incidence rates of tuberculosis are now more than 1% per year in many crowded urban settings with high rates of HIV, so prevalence rates might be high enough to make the yield of such a programme worthwhile. Such an approach would be expected to make a significant impact on transmission in the short term.

Another approach would be to enhance case finding in specific groups among whom rates of tuberculosis are higher than the general population. Studies conducted at voluntary counselling and testing centres, including those for antenatal mothers, have consistently demonstrated high numbers of tuberculosis cases who have not been diagnosed by passive case finding.^{49,50} Institutions such as prisons, hospitals and mines have also demonstrated high rates of tuberculosis transmission that could be reduced by more active screening and case detection.^{51–53} Households of tuberculosis patients have high rates of tuberculosis transmission.^{54–56} HIV-positive individuals with tuberculosis are less infectious than their HIV-negative counterparts but their household contacts also have a high HIV prevalence and are at high risk of tuberculosis.^{57,58} Thus, the households of HIV-positive tuberculosis patients, who make up 75% of urban tuberculosis in most cities in Southern Africa, are an attractive target for enhanced case-finding.

One of the strengths of the DOTS strategy is that it provides a framework not only to find the infectious cases but also to ensure that they are cured. The same overburdened health services that find it difficult to find cases efficiently will also find it difficult to support patients throughout treatment to achieve a cure. For this reason, DOTS programmes emphasize the need to raise the cure rate before embarking on programmes to increase the number of cases. Finding extra cases through active or enhanced case-finding will prove to be a disaster if such cases are not treated effectively. The result will be more chronic transmitters⁵⁹ in the community and a rising level of drug resistance.

If government health services cannot cope due to the overwhelming demand for care and decreasing resources, what can be done? Alternative health care providers exist in the form of traditional healers, community-based organizations and private practitioners. There are many examples of tuberculosis programmes working in synergy with these groups for both case-finding and case-holding services. In Lusaka, over half of all tuberculosis patients receive care from community-based organizations.⁶⁰ In Thyolo district in Malawi, the district tuberculosis services are strengthened and new interventions supported by a big international

NGO.⁶¹ The Catholic Diocesan Project in the Zambian Copperbelt provides a holistic approach to HIV that includes improved tuberculosis control.⁶²

Reducing the risk of reactivation

In areas of high tuberculosis incidence, up to 80% of the population may be latently infected with tuberculosis. Treatment of latent infection with tuberculosis preventive therapy has been demonstrated to reduce tuberculosis in both HIV-negative⁶³ and HIV-positive individuals.⁶⁴ Current WHO recommendations are that in settings with such a high prevalence of dual infection, all HIV-infected individuals should be offered tuberculosis preventive therapy if they can undergo adequate screening to avoid its use in cases of active disease.⁶⁵ In fact, the lack of widespread HIV counselling and testing services and the challenges of how to exclude people who already have active tuberculosis, means that the use of preventive therapy is not routine in any high burden country. Unless the scale of preventive therapy services can be expanded greatly, this intervention will be of limited benefit as a tool to reduce the burden of tuberculosis. However, for the individual living with HIV it is one of the few interventions proven to reduce morbidity in the absence of antiretroviral therapy.

On the other hand, as discussed above, people living with HIV have high rates of active tuberculosis and so are obvious targets for enhanced case-finding. Programmes that aim to start people on preventive therapy will need to implement an effective enhanced case-finding process at the same time and thus increase the benefits of the programme. The challenge both for preventive therapy programmes and for active case-finding programmes, outlined above, is how to diagnose or exclude tuberculosis in the absence of reliable diagnostic tools. Studies in South African gold mines suggest that in order to maximize the yield of screening it is necessary to culture sputum from all miners, including those who deny symptoms or have normal chest radiographs.⁴⁷ In contrast, studies based at Voluntary Counselling and Testing centres in Botswana, Uganda and Zambia suggest that the rate of tuberculosis is very low among those people who are HIV positive but have no symptoms.⁶⁶⁻⁶⁸ Investigators in all these sites felt comfortable to stop performing chest radiographs on asymptomatic clients prior to commencing preventive therapy.

Another unresolved question is the durability of the efficacy of preventive therapy. Prior to HIV, it

was possible to give a limited course of preventive therapy and still demonstrate an effect many years later.⁶³ However, in two African studies, the efficacy of 6 months of isoniazid waned over the next couple of years.^{69,70} The same studies produced different results when considering shorter rifampicin-based regimens. In Zambia, there was no detectable difference between the cohort receiving isoniazid compared to rifampicin and pyrazinamide, whereas in Uganda the efficacy of preventive therapy persisted for longer in those receiving rifampicin-based regimens. People living with HIV in high prevalence tuberculosis settings are at considerable risk of infection or reinfection with rapid progression to active disease.¹⁷ Long-term isoniazid might therefore serve as chemoprophylaxis as well as treating latent infection, but the efficacy of such an approach has not yet been documented.

An intervention that may prove to be greatly beneficial in reducing reactivation of tuberculosis in individuals is the use of antiretroviral drugs. These drugs are vitally important for people living with HIV but have been largely unaffordable in high burden countries. Studies from Brazil and South Africa show a benefit in terms of reduction of tuberculosis incidence.^{71,72} The costs of the drugs themselves have fallen hugely to less than \$500 per person per year. Whether costs will continue to fall further is less clear and the infrastructure needed to cope with this intervention is not yet available in most countries. The challenges of adherence and stock control faced by tuberculosis control programmes will be magnified many times as widespread antiretroviral therapy is implemented. Furthermore, it is by no means clear that the impact on tuberculosis will be positive. It is unlikely that antiviral therapy will lead to a full restoration of immunity and even milder immunodeficiency is associated with significantly increased risks of developing tuberculosis.⁷³ Thus, the impact of widespread antiretroviral therapy may be to increase the number of people in a community who are mildly immunocompromised and the incidence of tuberculosis at a community level might rise.⁷⁴

Reduction in HIV transmission

Many strategies have been proposed or even proven to reduce HIV transmission in various situations. Any strategy that successfully reduces HIV transmission will benefit tuberculosis control, since around a third of all HIV-positive individuals will develop tuberculosis before they die. However, in

the context of the combined epidemics of tuberculosis and HIV, two strategies require specific discussion, implementation of antiretroviral drugs and voluntary HIV testing. As discussed above, antiretroviral therapy will have direct effects on tuberculosis and their implementation shares many programmatic aspects with tuberculosis.⁷⁵ Voluntary HIV testing identifies HIV-positive individuals who are a target for both enhanced tuberculosis case-finding and for tuberculosis preventive therapy.

Antiretroviral therapy can dramatically reduce plasma levels of HIV, which correlate closely with infectivity.⁷⁶ Individuals taking antiretroviral drugs, whose viral load is suppressed, are therefore likely to be much less infectious. On the other hand, only a small proportion of the HIV-positive population require antiretroviral therapy and an even smaller proportion will actually be taking it, so the effect on HIV transmission at a population level may be small. Furthermore, acute HIV infection and seroconversion are associated with high viral loads but rarely detected and often not treated. Patients on antiretroviral drugs live longer and so their cumulative risk of transmitting infection may be higher, particularly if they feel that the risk of transmission is low because they are being treated. In rich countries, there is no evidence that the widescale provision of antiretroviral drugs has led to a fall in HIV incidence at a community level.⁷⁷ However, in poor countries with generalized HIV epidemics, stigma is believed to be a major impediment to HIV prevention programmes. It is likely that the provision of better care, including antiretroviral drugs will reduce the fear and stigma surrounding HIV and this could lead to substantial benefits in terms of reduced transmission.

Voluntary counselling and testing has been compared to health information alone in a randomized trial in Kenya, Tanzania and Trinidad. People who accepted HIV testing with counselling were more likely to change their sexual behaviour in ways predicted to reduce HIV transmission.⁷⁸ Indeed, economic evaluation suggests that this intervention should be one of the main pillars of any HIV prevention programme.⁷⁹⁻⁸¹

Operationalizing tuberculosis/HIV activities

How do we put all of these activities together? The ProTEST project has been one example of the operationalization of the combined tuberculosis/HIV reduction activities that have been mentioned.⁸² ProTEST uses enhanced VCT as an entry

point for a series of activities that aim to reduce HIV transmission and tuberculosis incidence. The provision of services for people living with HIV acts as an incentive for more of the community to access VCT. HIV-negative individuals can receive education, condoms and also services to detect and treat STIs to help prevent HIV transmission. HIV-positive individuals receive those same services but in addition undergo enhanced screening for tuberculosis, receive tuberculosis preventive therapy and also diagnosis and treatment of opportunistic infections. In some of the pilot sites, antiretrovirals are available for the prevention of mother to child transmission of HIV and it is hoped to include antiretrovirals for treatment in the near future.

ProTEST pilot sites exist in Zambia, Malawi, Uganda and South Africa and phased implementation is planned for these countries as well as Ethiopia, Tanzania and Kenya. The lessons learnt from these sites are vital for the expansion and implementation of similar tuberculosis/HIV activities. The philosophy of the ProTEST initiative is to act as the cement between existing tuberculosis and HIV stakeholders at all levels, encouraging dialogue and sharing of resources to maximize the impact that the individual activities can have alone.

Traditionally, tuberculosis programmes and HIV programmes came from different perspectives. Tuberculosis programmes worked in a vertical manner with a top down medical approach and most activities based in the district hospital. HIV programmes have worked in a more multisectoral manner with more emphasis on community and education. Increasingly however, tuberculosis programmes are moving closer to the client with decentralized diagnostic centres in larger peripheral clinics and with supervision of treatment within the local community or even in the home.⁸³ At the same time, the emphasis of HIV programmes is shifting to include more basic care delivered at clinics and in the home as well as the possibility of antiretroviral therapy based on a medical model delivered through district or specialized clinics. The convergence of these two approaches can only benefit the tuberculosis and HIV control activities by each accentuating its strengths and learning from the other.

The way forward—can we control tuberculosis in high HIV prevalence settings?

The recent commission on macroeconomics and health has emphasized the huge gains that might be

made to improve the health outcomes of the poor if a rather limited set of interventions was scaled up and sufficient investment provided to strengthen the health system to deliver them.⁸⁴ To control tuberculosis in high HIV prevalence settings, we must strengthen health systems to include not only expansion of the DOTS strategy but also full-blooded implementation of voluntary counselling and testing, enhanced and active tuberculosis case-finding, preventive therapy and better care for people living with HIV including antiretroviral therapy. ProTEST and other tuberculosis/HIV pilot projects have demonstrated that combining the strengths of tuberculosis and HIV programmes is feasible and the new strategic framework to decrease the burden of tuberculosis/HIV released by the STOP TB partnership guides countries towards wider implementation.⁸⁵ Several countries have used this framework to help to develop their proposals for support from the Global Fund to Fight AIDS, Tuberculosis and Malaria.

The approach needed to control tuberculosis needs to be integrated into broader development and poverty reduction goals. Investment in educating girls, for instance, is likely to have a direct impact on the incidence of HIV,⁸⁶ which in turn has a direct impact on the incidence of tuberculosis. While the scale of the investment seems large to those used to the inadequacy of national health budgets, the coalition of interested partners, bilateral, multilateral and non-governmental is growing.

Nelson Mandela pointed out to the delegates at the international conference on AIDS in Durban in 2000 that "a tragedy of unprecedented proportions is unfolding in Africa. AIDS today in Africa is claiming more lives than the sum total of all wars, famines and floods, and the ravages of such deadly diseases as malaria. It is devastating families and communities, overwhelming and depleting health care services, and robbing schools of both students and teachers." We need to galvanize the orators to transform rhetoric into action.

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